NATIONAL HUMAN GENOME RESEARCH INSTITUTE Division of Intramural Research

The Rich Resources of Mouse Genetics

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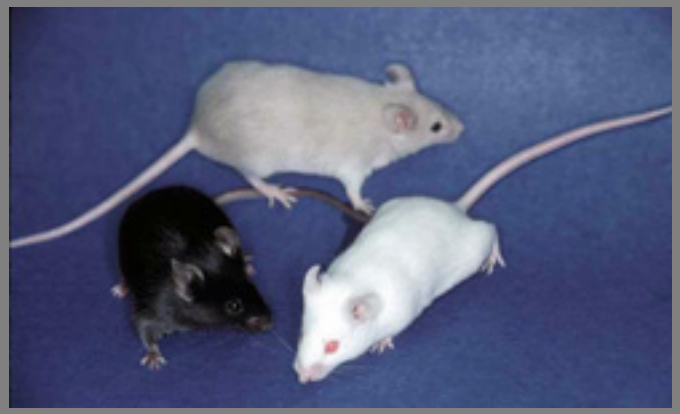
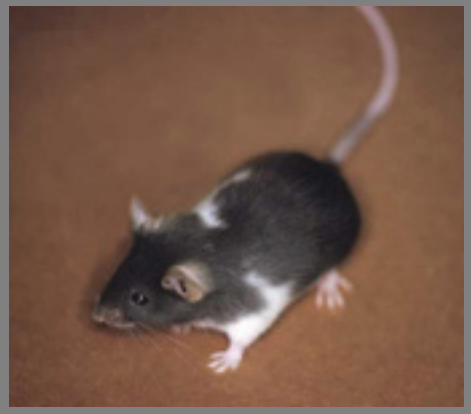
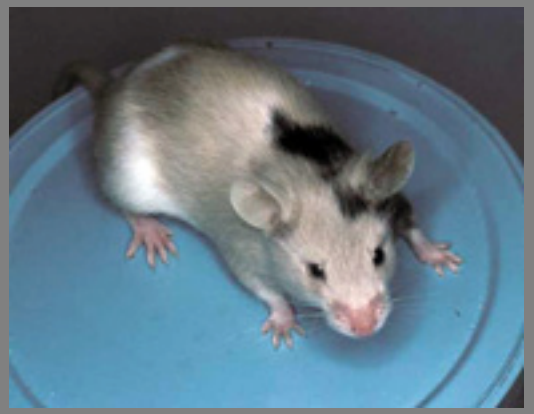




Outline

- History of Mouse Genetics
- The Mouse Genome
- Reverse Genetics: Engineered Mice
- Forward Genetics: Screens for Induced Mutations
- Strategic Breeding for Diversity
- Public Database Resources

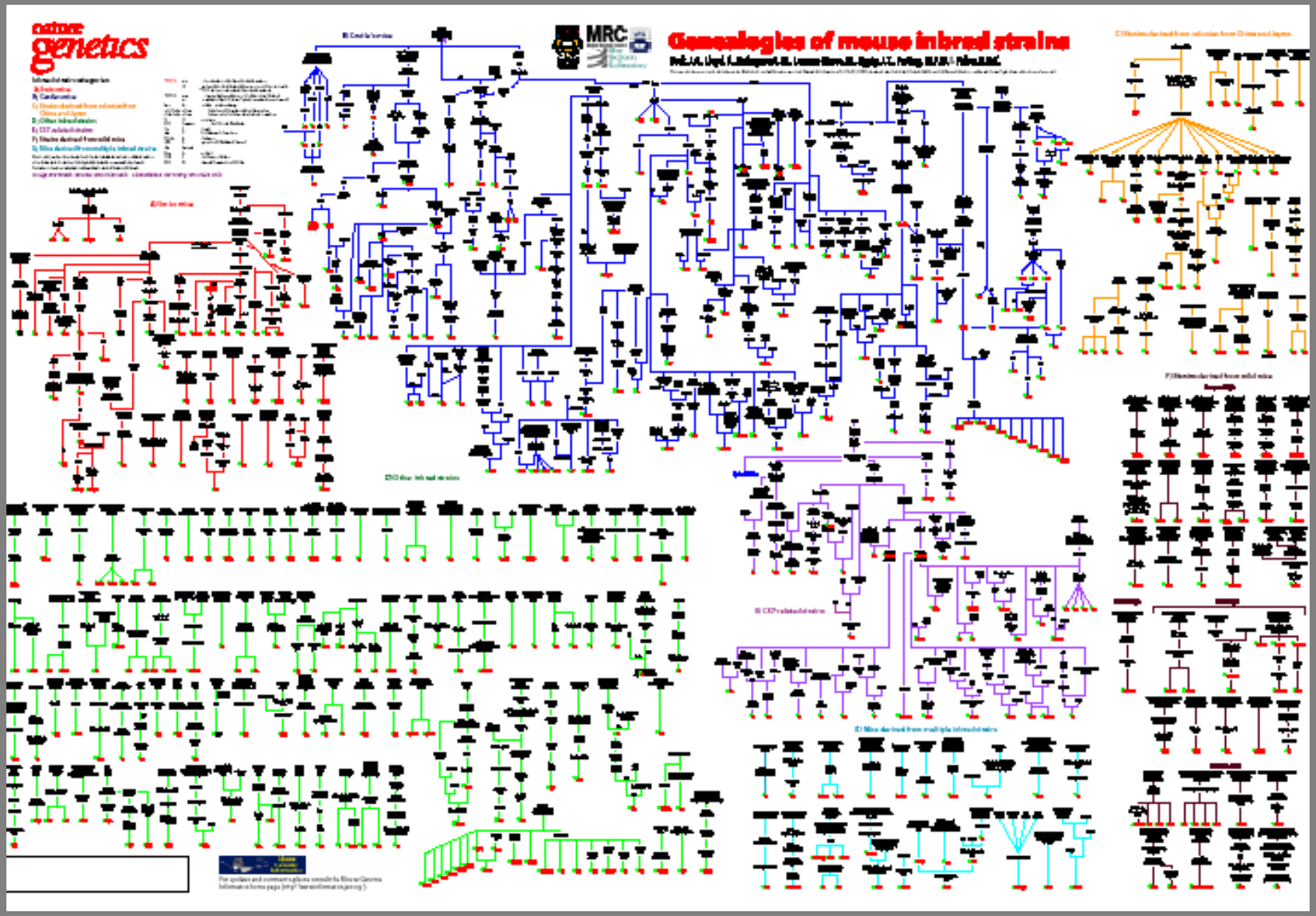
History of the Laboratory Mouse

- 1100 BC "Fancy" mouse breeding of coat color variants in Asia & Europe
- 1900 Retired schoolteacher Abbie Lathrop breeds fancy mice in Granby, MA
- 1909 first inbred strains established
- 1929 The Jackson Laboratory founded
- 1962 nude mouse
- 1980 first transgenic mouse
- 1989 first knockout mouse
- 1990 explosion of engineered mice & beginning of mouse genome project

Mouse Stocks

- Outbred Stocks
  - Genetically undefined, bred to maintain heterozygosity
  - Cheap & healthy for when genotype does not matter
  - Should not be used for breeding experiments
- Inbred Strains
  - Bred for homozygosity (>100 strains available)
- Several commercial vendors available
  - JAX (jaxmice.jax.org)
  - Taconic (www.taconic.com)
  - Charles River (www.criver.com)

Inbred Strain Geneologies



Nature Genetics **24**:23-25 (2000)

Mouse Phenome Database

All phenotype strain survey data > blood chemistry > glucose

Plots & tools wizard

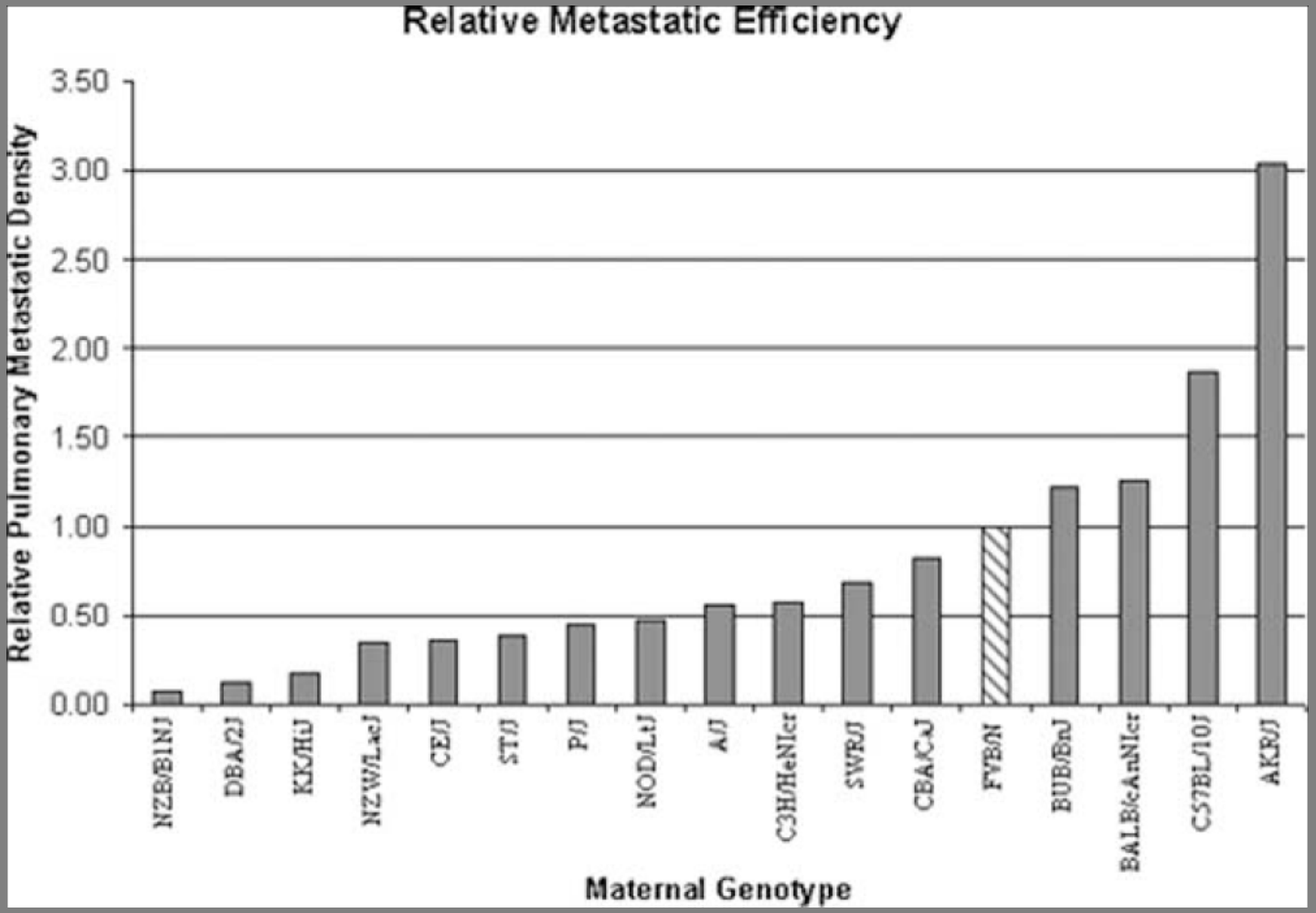
Change list style | Display strain values | Compare 2 strains | Specific strain panels

blood chemistry — glucose

Eumorphia1	glucose (plasma GLU) [mg/dL]	6 strains age 12wks
Jaxpheno3	glucose (plasma GLU, 4hr fast) [mg/dL] • age 8wks • age 16wks age comparison	11 strains ages: see details
Naggert1	glucose (plasma GLU, 4hr fast) [mg/dL] baseline and high-fat diet 17wks • baseline • after 17wks on diet • Δchange after diet diet effect comparison	43 strains age 7-9wks at baseline
Lake1 B6.A consomic	glucose (plasma GLU, 4hr fast) [mg/dL]	23 strains age 8wks
Svenson2 B6.PWD consomic	glucose (plasma GLU, 4hr fast) [mg/dL]	18 strains age 8wks
QTL-Reifsnyder1 BC1 (NON | NZO)	QTL analysis data set: Body weight, composition, glucose, insulin and leptin	N=204 age 4-24wks ♂
QTL-Smith1 F2 (B6 | CAST)	QTL analysis: Fat, carbohydrate, and calorie intake 2-choice macronutrient diet 10d	N=502 age 9-13wks ♂

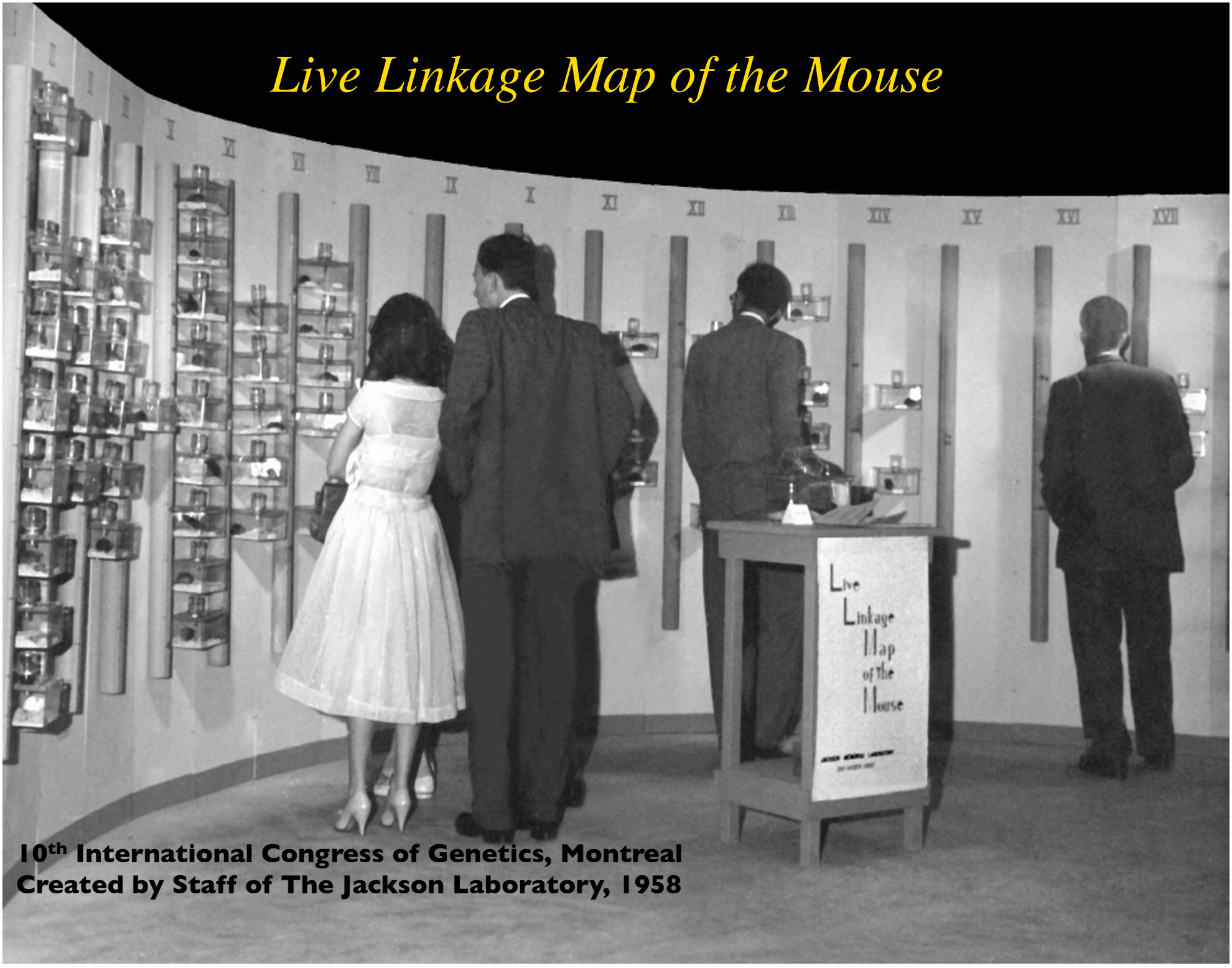
http://phenome.jax.org/pub-cgi/phenome/mpdcgi

Affect of Background Strain



T. Lifsted et al. *Int. J. Cancer* (1998) **77**:640-644
K. Hunter. *Canc Letter* (2003) **200**:97-105

Live Linkage Map of the Mouse

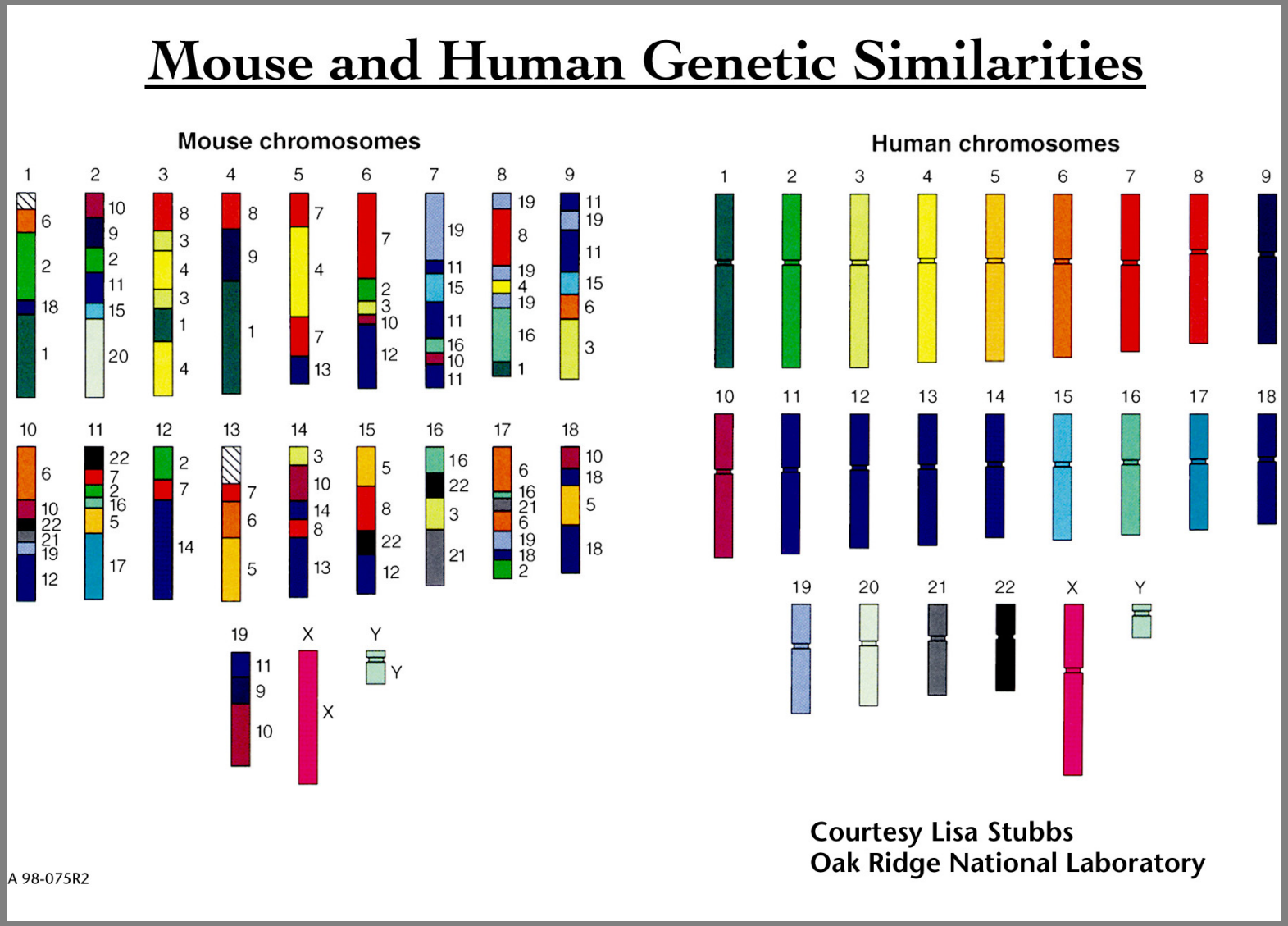


10th International Congress of Genetics, Montreal
Created by Staff of The Jackson Laboratory, 1958

The Mouse Genome

Nature **420:**520-562 (2002)

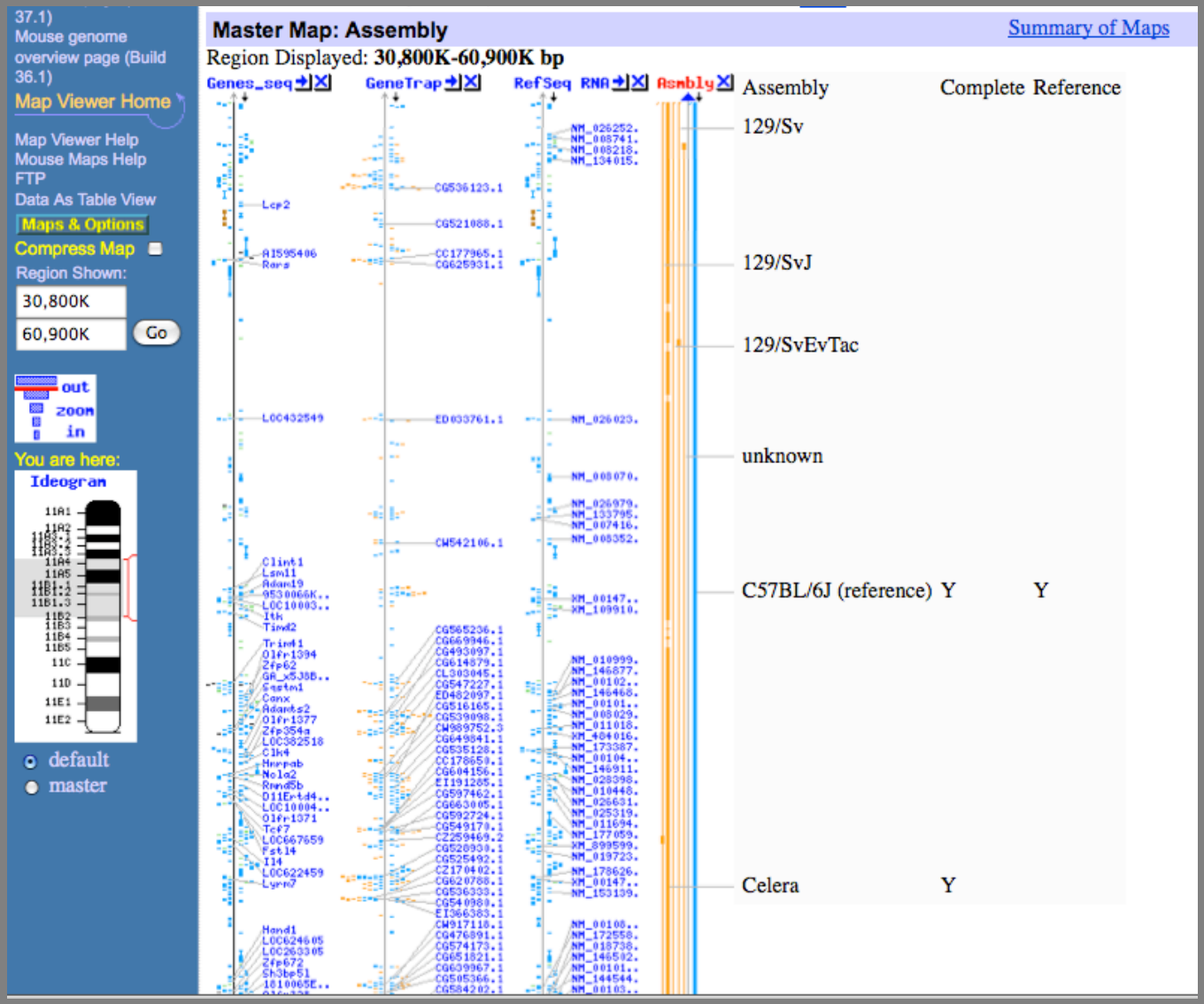
Synteny


Mouse and Human Genetic Similarities
Mouse chromosomes
1 6 2 18 1
2 10 9 2 11 15 20
3 8 3 4 3 1 4
4 8 9 1
5 7 4 7 13
6 7 2 3 10 12
7 19 11 15 11 16 10 11
8 19 8 19 4 19 16 1
9 11 19 11 15 6 3
10 6 10 22 21 19 12
11 22 7 2 16 5 17
12 2 7 14
13 7 6 5
14 3 10 14 8 13
15 5 8 22 12
16 16 22 3 21
17 6 16 21 6 19 18 2
18 10 18 5 18
19 11 9 10
X X
Y Y
Human chromosomes
1 2 3 4 5 6 7 8 9
10 11 12 13 14 15 16 17 18
19 20 21 22 X Y
A 98-075R2
Courtesy Lisa Stubbs
Oak Ridge National Laboratory

The Mouse Genome

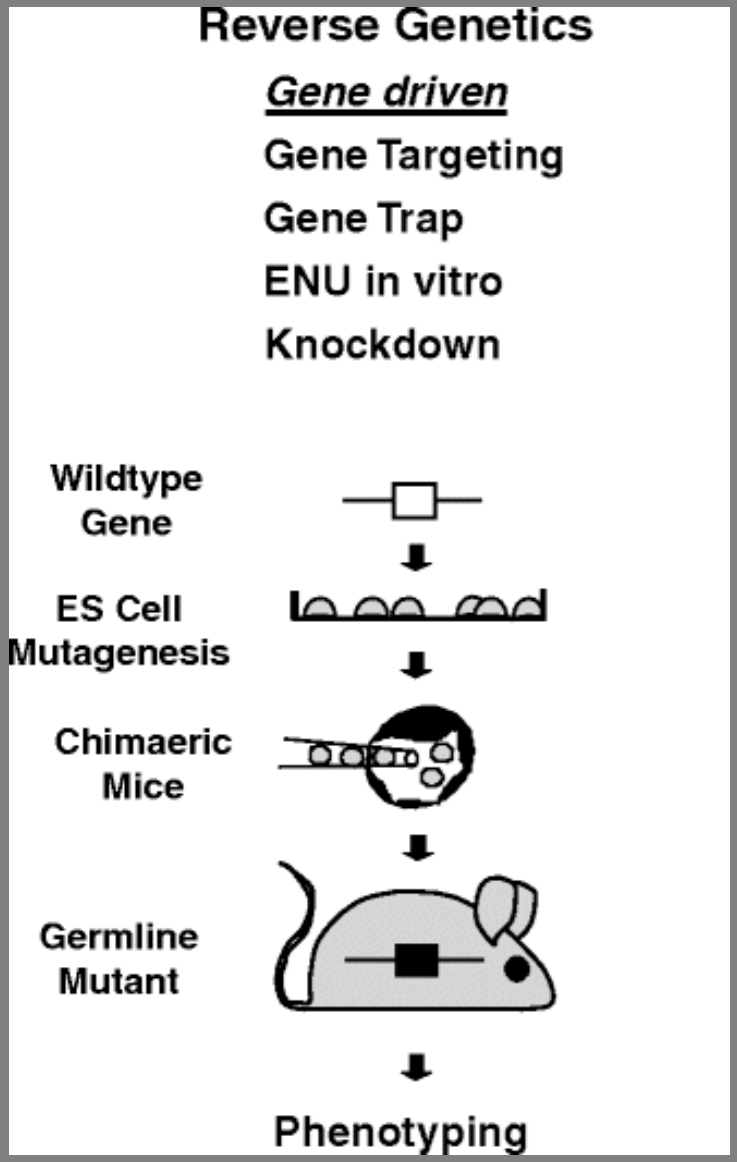
- 19 autosomes, XY
- NCBI Build 37
  - 2.66 x 10^9 bp
    - 124 contigs mostly >5000 kb
  - 28,278 transcripts
  - C57BL/6J is reference strain
- Web browsers
  - http://genome.ucsc.edu
  - http://www.ensembl.org
  - http://www.ncbi.nlm.nih.gov
    - Includes alternate partial assemblies

The Mouse Genome



http://www.ncbi.nlm.nih.gov/projects/mapview/

Strategies to identify gene function



From: Gene Knockout Protocols

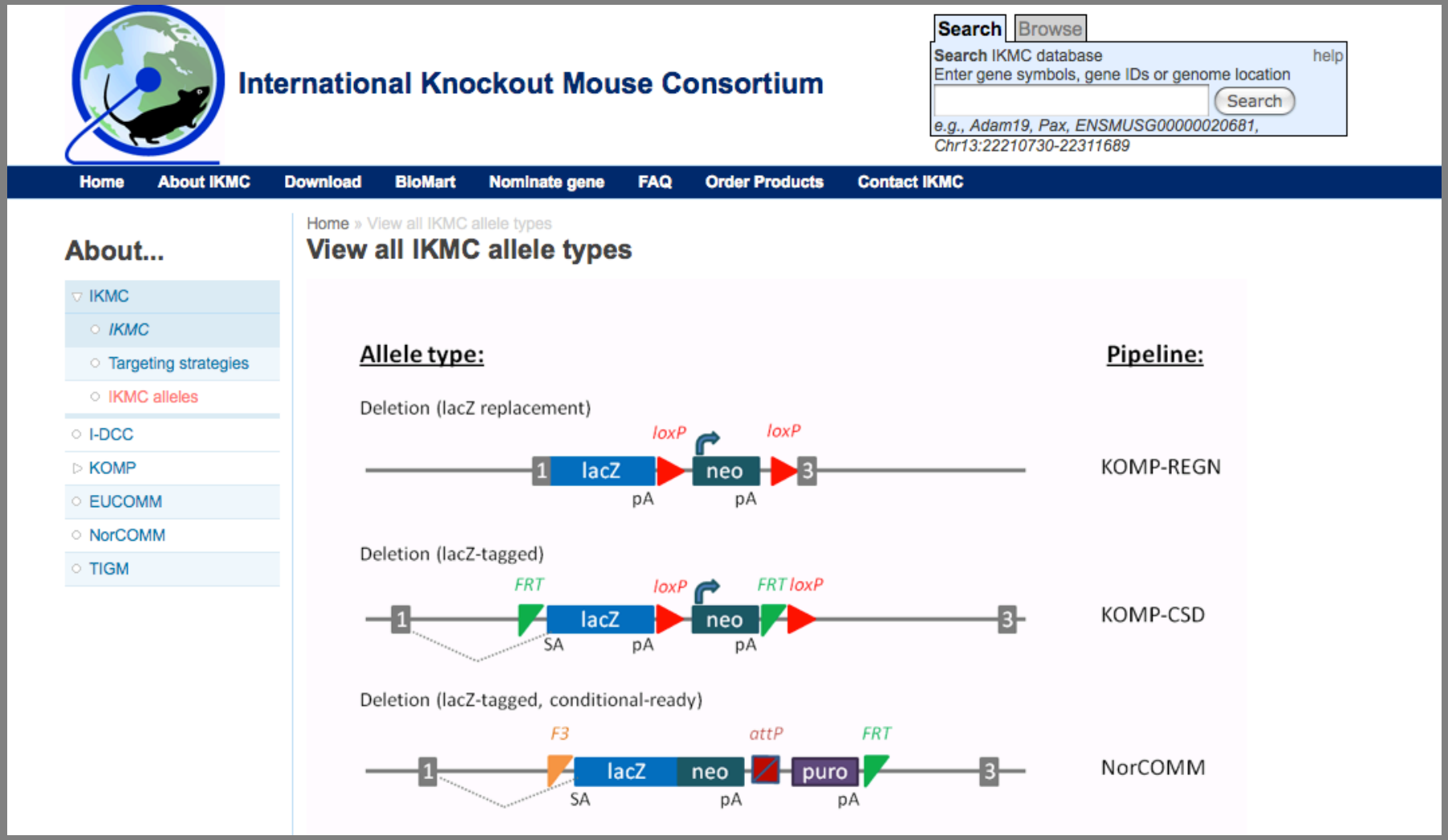
Large Scale Efforts

IKMC Gene Progress Summary

Total Genes	KOMP		EUCOMM	NorCOMM	TIGM
	CSD	Regeneron			
Project goal	5000	3500	8000	500	-
Vectors generated	5099	3295	4477	312	-
Vectors available	4791	2296	4477	312	-
ES cells generated	2650	1808	2386	45	-
ES cells available	1940	1136	2386	45	10699
Mutant mice generated	168	160	279	0	-
Mutant mice available	168	71	279	0	-

http://www.knockoutmouse.org

Large Scale Efforts



http://www.knockoutmouse.org

Finding the Mice you Need

IMSR Summary

Query Summary
State equals live mouse
Gene/Allele Symbol/Name contains RAS searching Current/Synonyms
Display Limit equals 10000

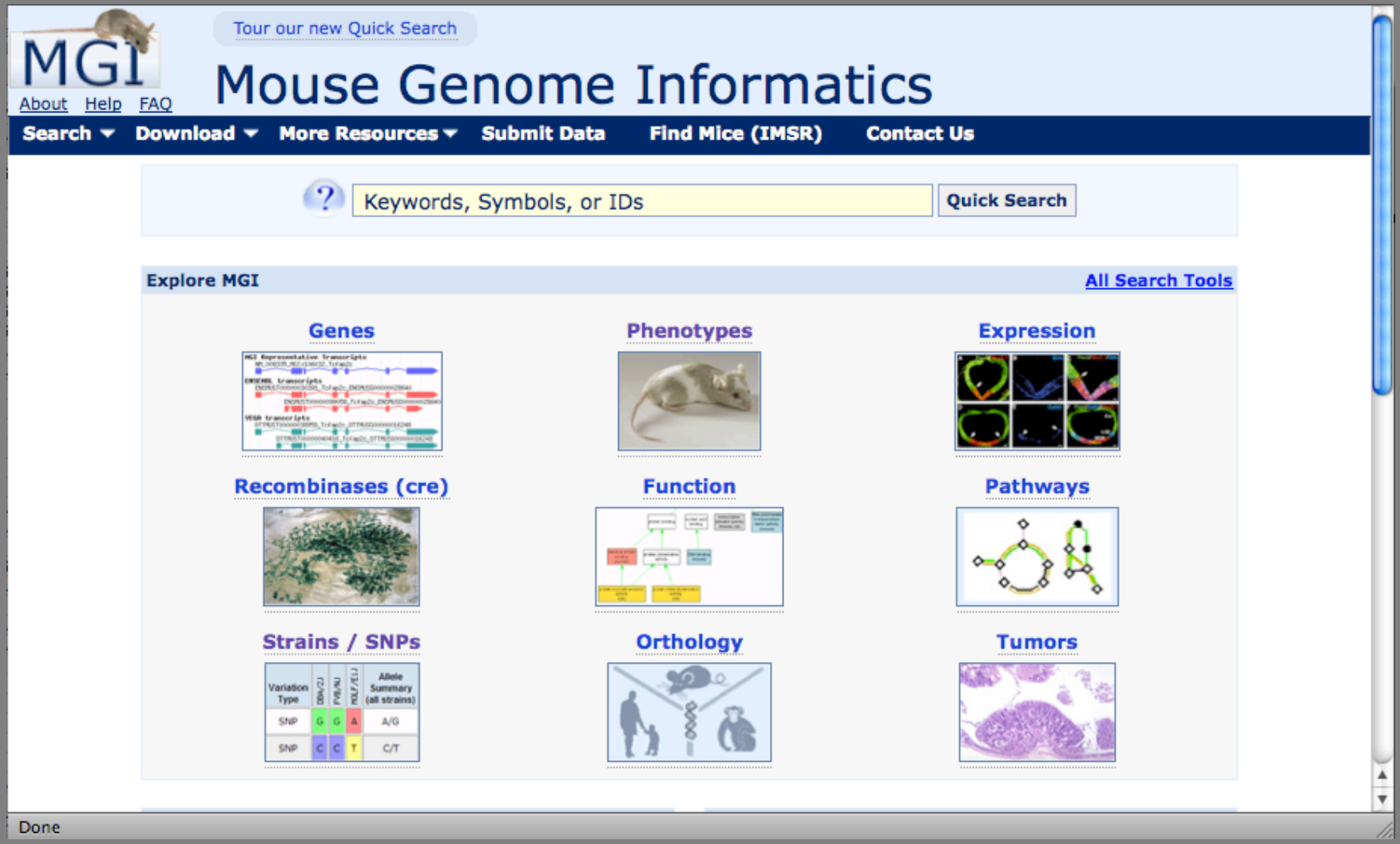
281 matching items displayed

\+ Name carries approved nomenclature.
\- Name does not carry approved nomenclature.
? Name has not been reviewed for nomenclature.

N	Strain/Stock Designation	Holder Site	State Key	Strain Type(s)	Strain/Stock Synonyms	Chr	Allele Symbol	Allele Name	Gene Name	Mutation Type(s)
+	129-Alpl$^{tm1(cre)Nagy}$/J	JAX	live	coisogenic strain		4	Alpl$^{tm1(cre)Nagy}$	targeted mutation 1, Andras Nagy	alkaline phosphatase, liver/bone/kidney	recombinase(cre/flp)
+	129P1/ReJ	JAX	live	inbred strain		10	Cdh23^{ahl}	age related hearing loss 1	cadherin 23 (otocadherin)	
						18	Poli^{d}	polymerase iota deficient	polymerase (DNA directed), iota	spontaneous mutation
						8	Disc1^{del}	deletion	disrupted in schizophrenia 1	spontaneous mutation
+	129P3/J	JAX	live	inbred strain, segregating inbred	129/J	10	Cdh23^{ahl}	age related hearing loss 1	cadherin 23 (otocadherin)	
						5	Rmcf^{r}	MCF resistant	resistance to MCF virus	spontaneous mutation
						8	Disc1^{del}	deletion	disrupted in schizophrenia 1	spontaneous mutation
						18	Poli^{d}	polymerase iota deficient	polymerase (DNA directed), iota	spontaneous mutation
+	129S-Parp1^{tm1Zqw}/J	JAX	live	mutant strain	129S-Adprt1^{tm1Zqw}/J, 129S-Aprt^{tm1Zqw}, 129S-Aprt^{tmZqw}	1	Parp1^{tm1Zqw}	targeted mutation 1, Zhao-Qi Wang	poly (ADP-ribose) polymerase family, member 1	targeted mutation
+	129S-Top2b^{tm2Jcw}/J	JAX	live	coisogenic strain		14	Top2b^{tm2Jcw}	targeted mutation 2, James C Wang	topoisomerase (DNA) II beta	targeted mutation
+	129S6.CB(B6)-Del(1)1Brk Gpi1^{b}/Gpi1^{c}/BrkMdfJ	JAX	live	congenic strain, mutant strain	129S6.CBA(B6)-Del(1)1Brk Gpi1^{b}/Gpi1^{c}/BrkMdfJ	1	Del(1)1Brk	deletion, Chr 1, Jane Barker 1	deletion, Chr 1, Jane Barker 1	chromosomal aberration
						7	Gpi1^{b}	b variant	glucose phosphate isomerase 1	

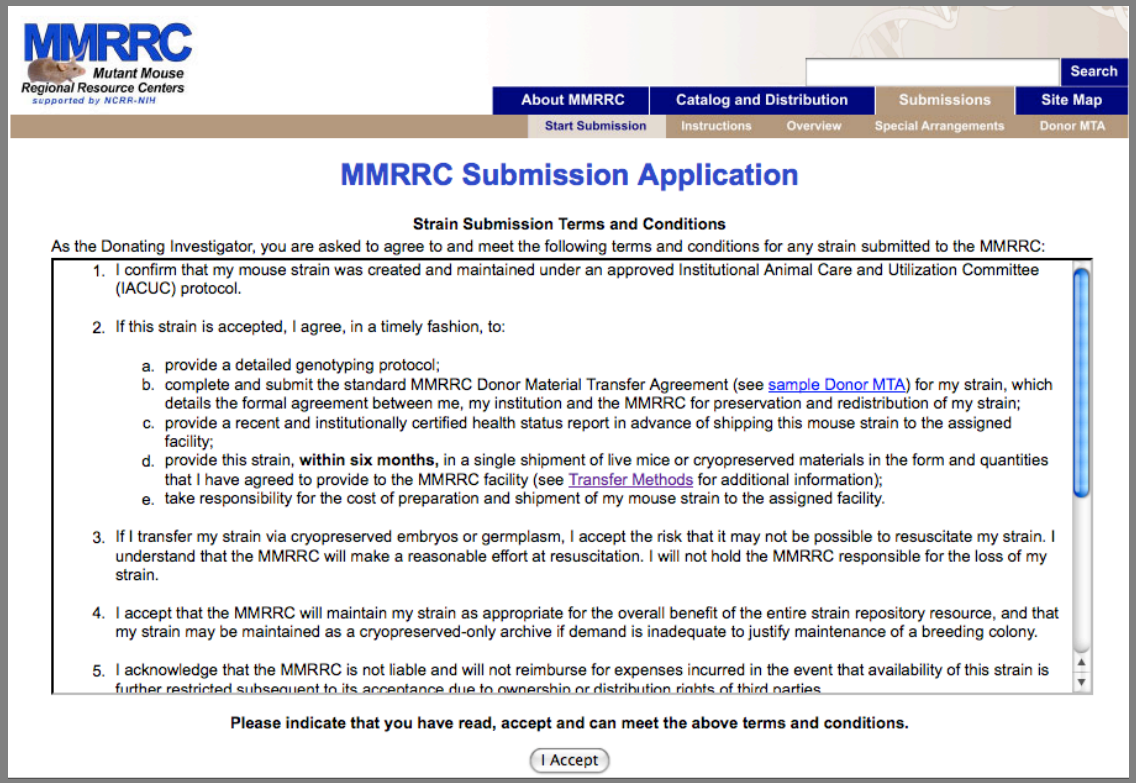
http://www.findmice.org

Database Resources



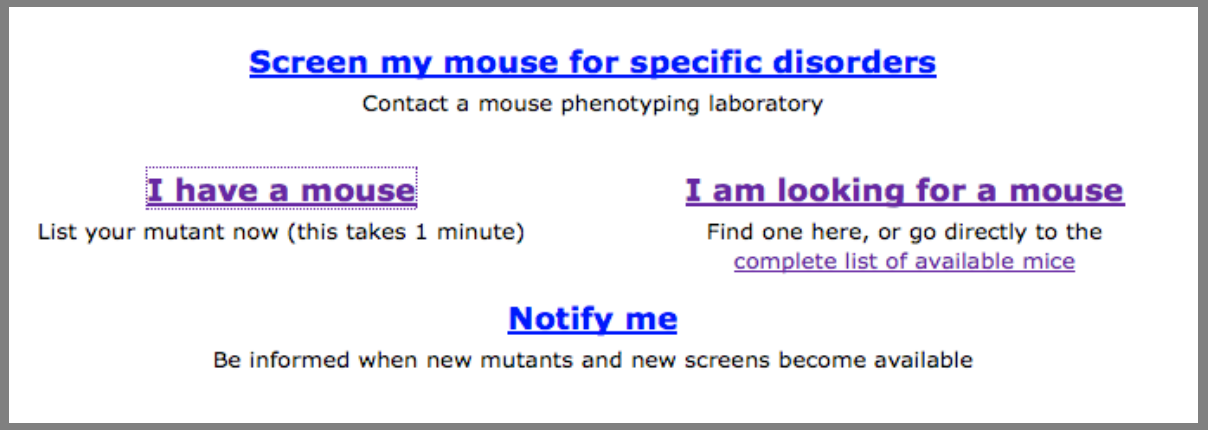
http://www.informatics.jax.org/

Sharing the Mice you Have

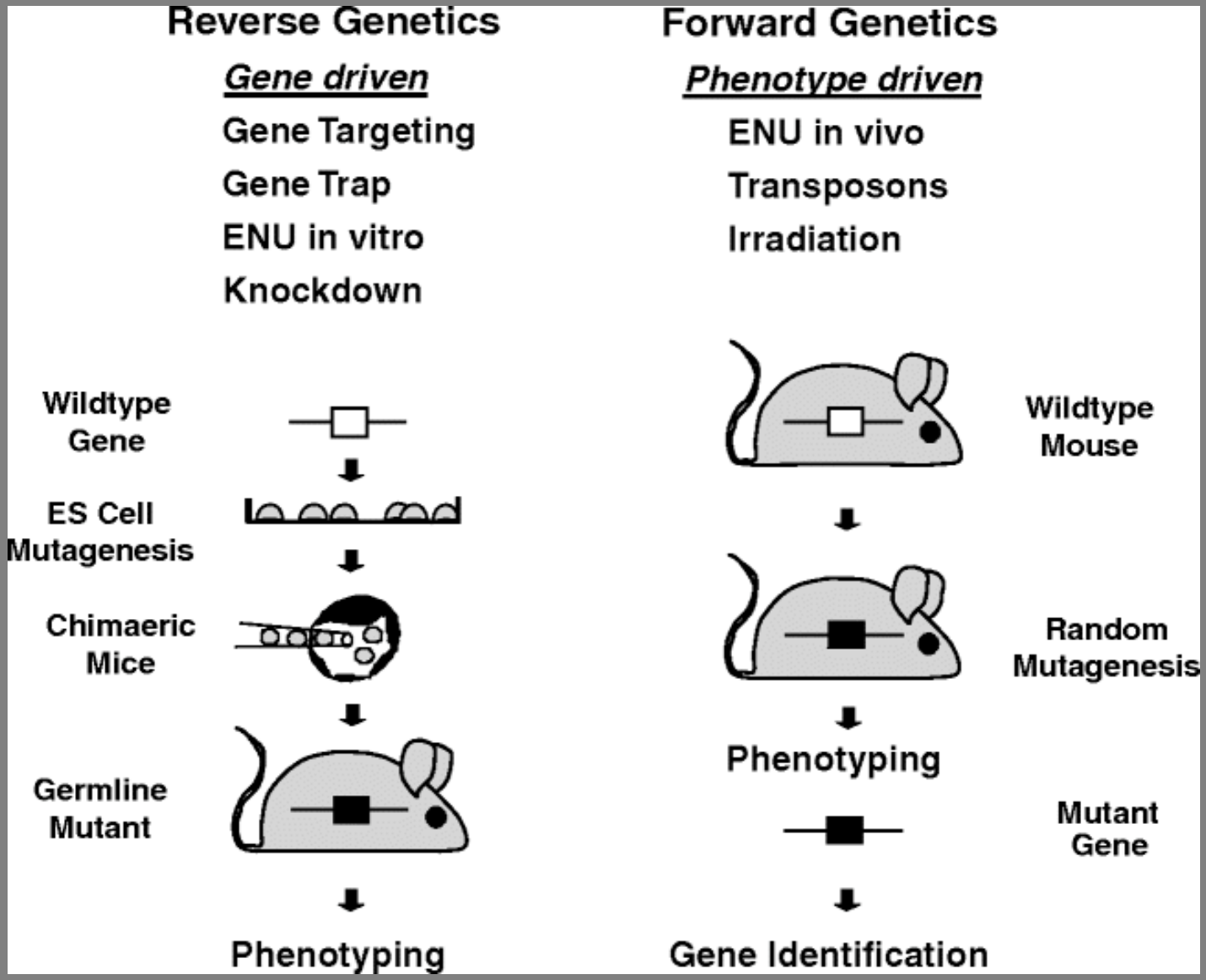


http://www.mmrrc.org

http://mymouse.org



Strategies to identify gene function

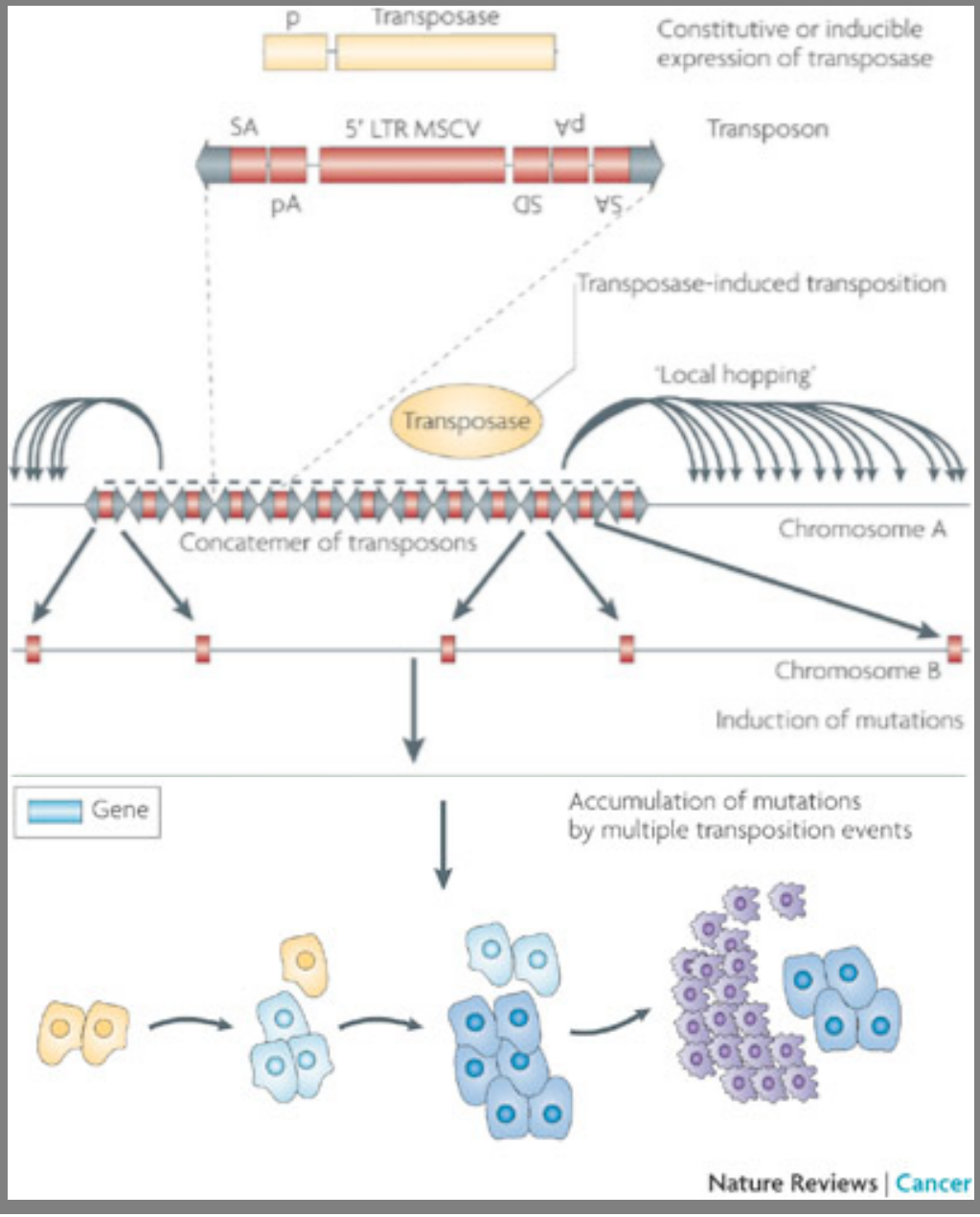


From: Gene Knockout Protocols

Forward Genetics

- *Retroviral Insertional Mutagenesis*
  - *MMTV, MuLV*
- *Transposon Mediated Mutagenesis*
- *ENU Mutagenesis*

Transposon Mediated Mutagenesis



Kool & Berns
Nature Reviews Cancer (2009) **9**:389-399.

Transposon Mediated Mutagenesis

- Sleeping beauty

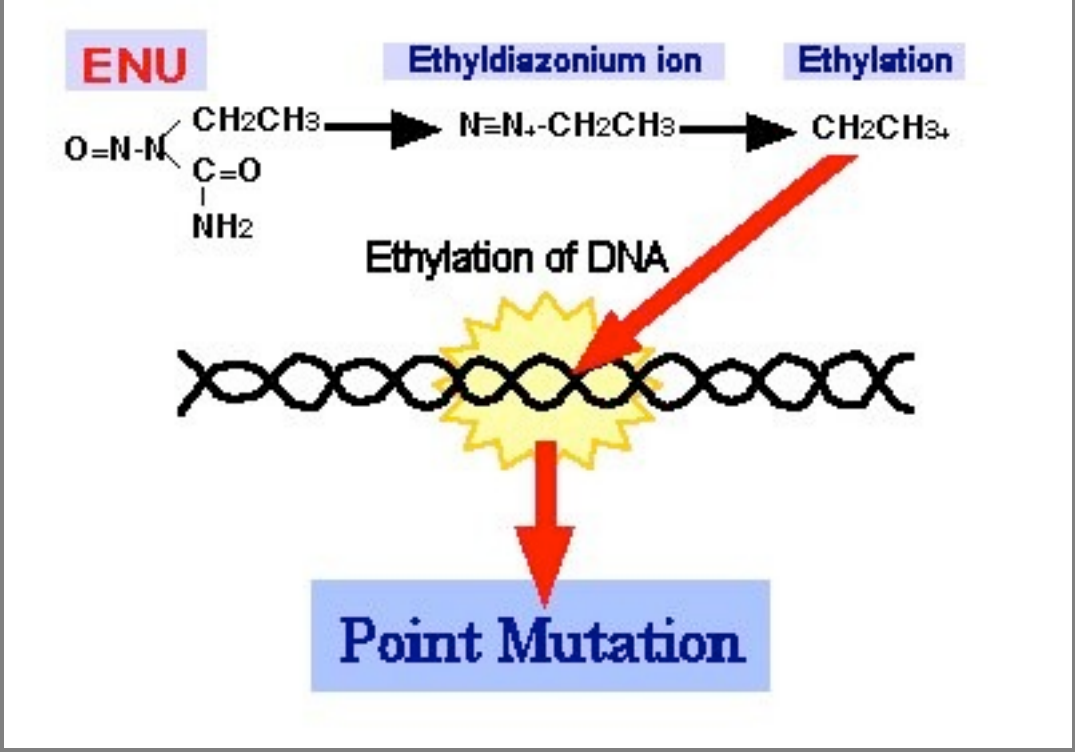
  Keng et al. (2005) *Nature Methods* **2**: 763-769

- piggyBac

  Dinget al. (2005) *Cell* **122**: 473-483

ENU Mutagenesis

- ENU mutagenesis (ethylnitrosourea)



- Alkylating agent
- Mutations introduced into spermatogonial stem cells

ENU Mutagenesis Large Scale Screens

Riken

broad phenotyping

MRC Harwell

broad phenotyping

The Jackson Laboratory

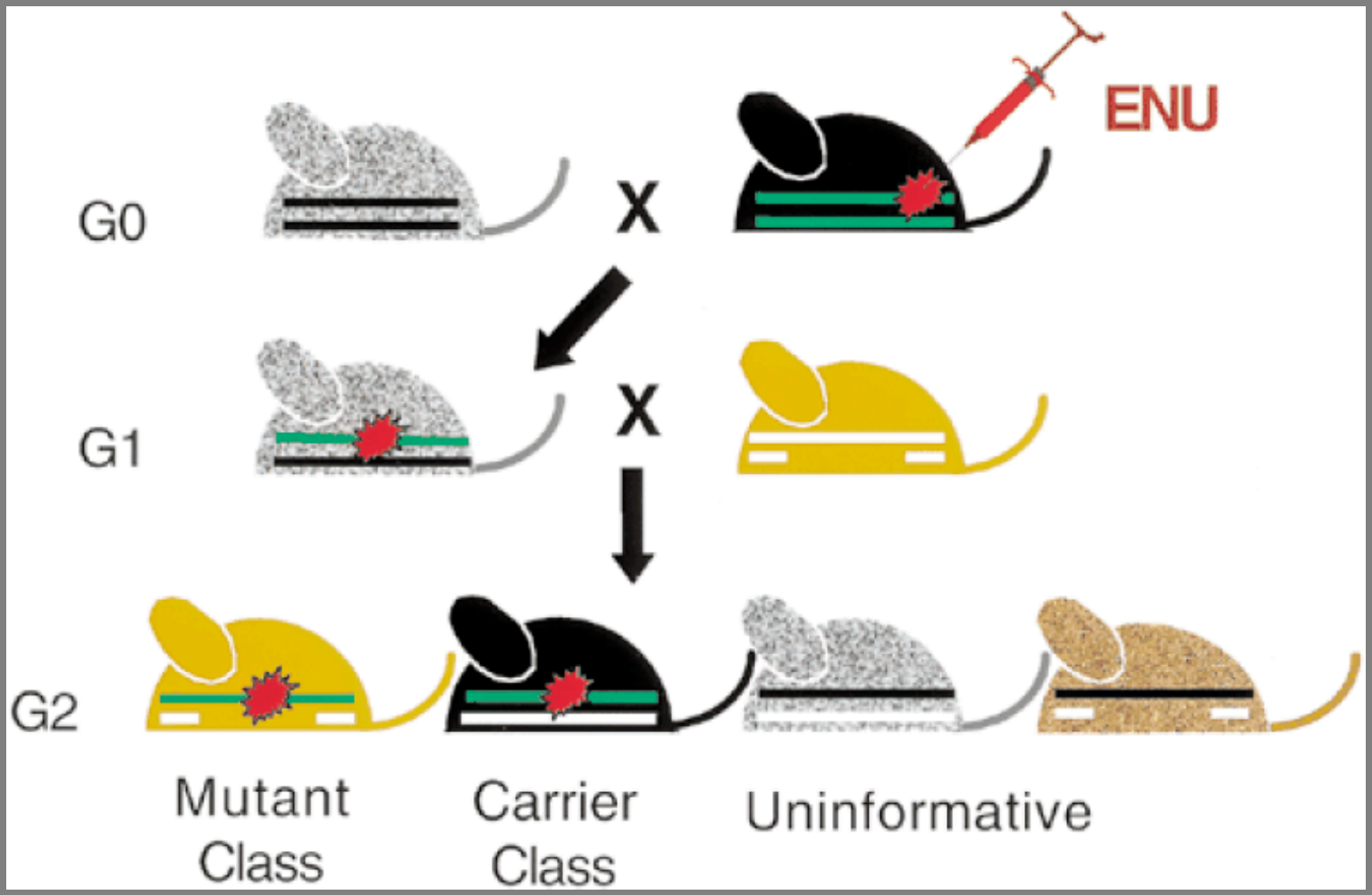
Neurological, reproductive, heart, lung, blood

Baylor College of Medicine

Chromosome 11

ENU Mutagenesis

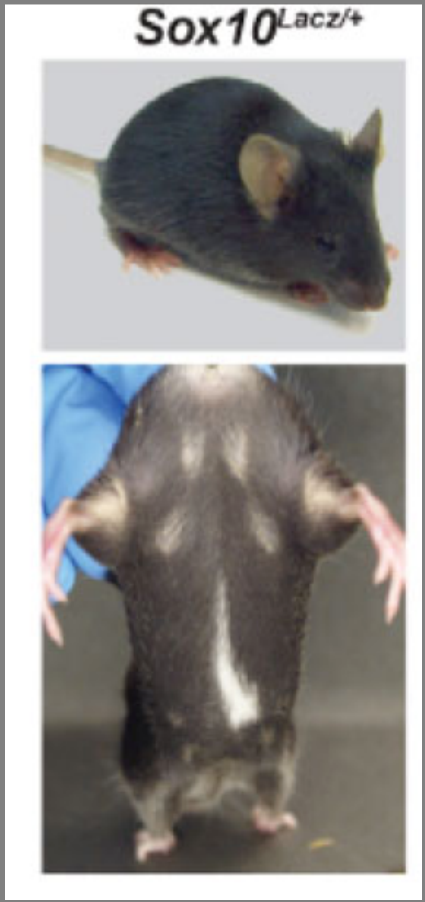
Region specific screens



Justice Hum Mol Gen (1999) **8:**1955-63

ENU Mutagenesis

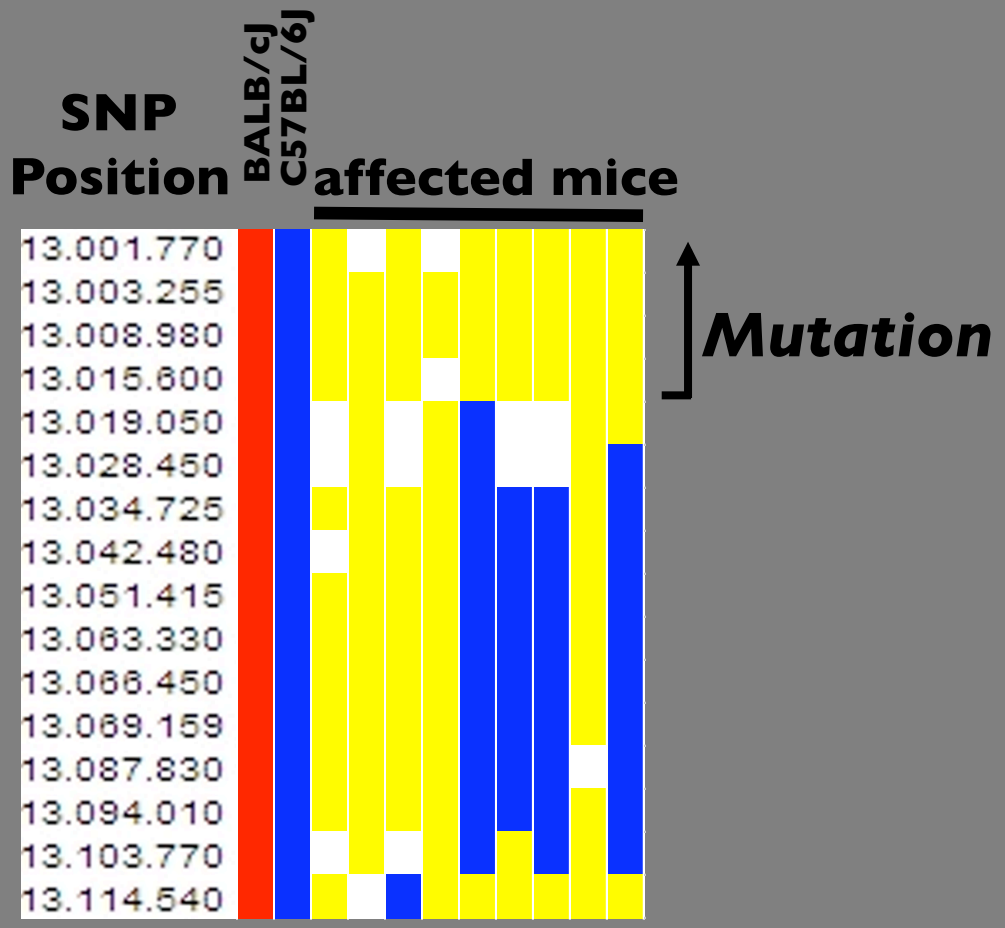
Sensitized/Modifier screens



Matera et al. Hum Mol Gen (2008) **17**:2118-2131

Mapping Phenotypes

SNP or SSLP markers polymorphic between the parental mouse strains (C57BL/6J and BALB/cJ) are used to genotype affected mice throughout the genome



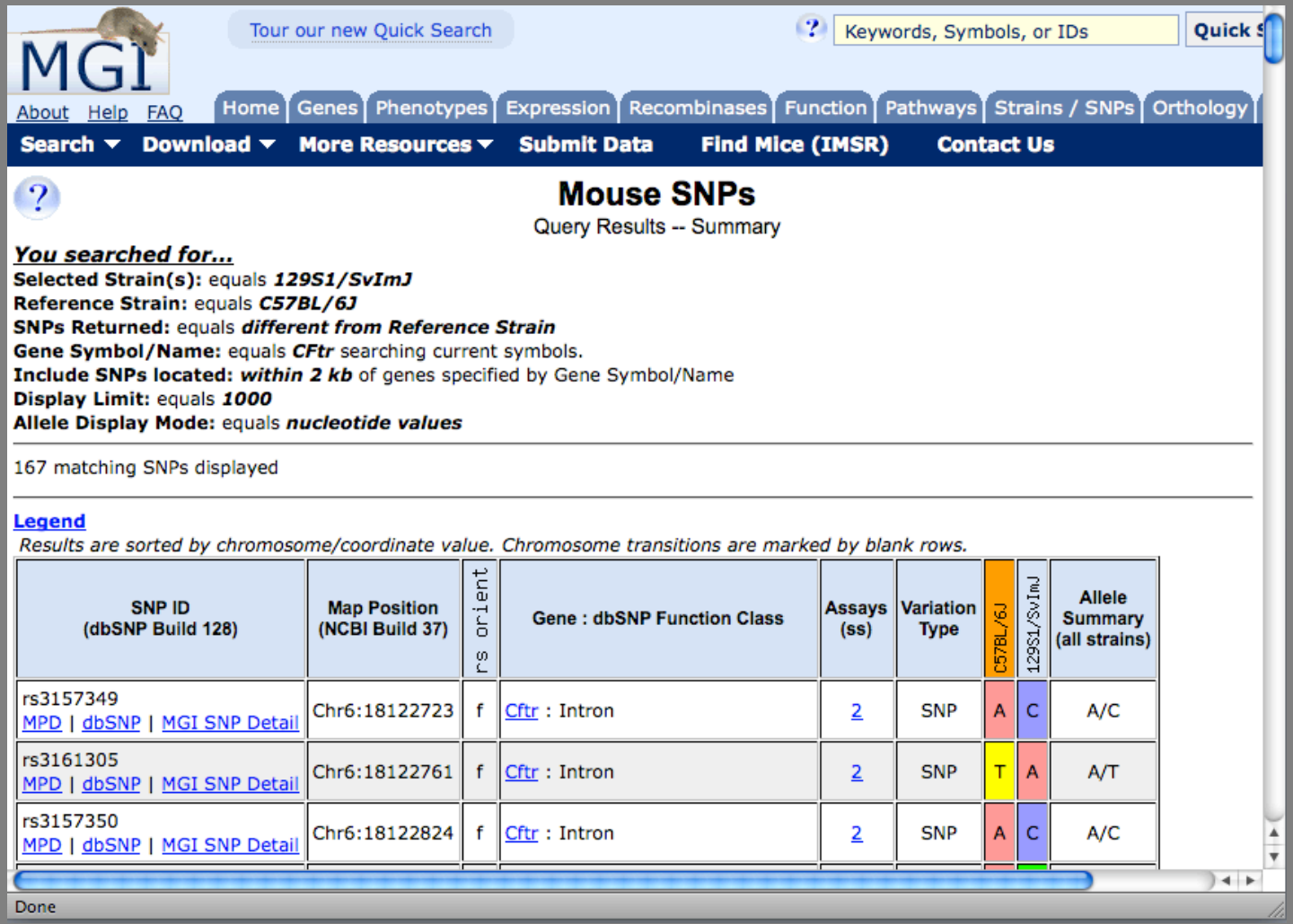
- **Homozygous BALB/cJ**
- **Homozygous C57BL/6J**
- **Heterozygote**
- **No call**

Polymorphic Variation

- RFLP
- Simple sequence length polymorphism (SSLP)
  - SSRP, STRP, Dinucleotide repeat, microsatellites
- Copy number variation (CNVs)
- Single Nucleotide Polymorphisms
  - Over 10,000,000 SNPs in NCBI dbSNP
  - From 86 strains

Searching for Polymorphic Variation

- http://phenome.jax.org & http://www.informatics.jax.org
- 167 SNPs polymorphic between B6 and 129 within 2 kb of Cftr



MGI

Tour our new Quick Search

Keywords, Symbols, or IDs

Quick S

About Help FAQ

Home | Genes | Phenotypes | Expression | Recombinases | Function | Pathways | Strains / SNPs | Orthology

Search ▾ Download ▾ More Resources ▾ Submit Data Find Mice (IMSR) Contact Us

Mouse SNPs

Query Results -- Summary

You searched for...

Selected Strain(s): equals ***129S1/SvImJ***
Reference Strain: equals ***C57BL/6J***
SNPs Returned: equals ***different from Reference Strain***
Gene Symbol/Name: equals ***CFtr*** searching current symbols.
Include SNPs located: ***within 2 kb*** of genes specified by Gene Symbol/Name
Display Limit: equals ***1000***
Allele Display Mode: equals ***nucleotide values***

167 matching SNPs displayed

Legend

Results are sorted by chromosome/coordinate value. Chromosome transitions are marked by blank rows.

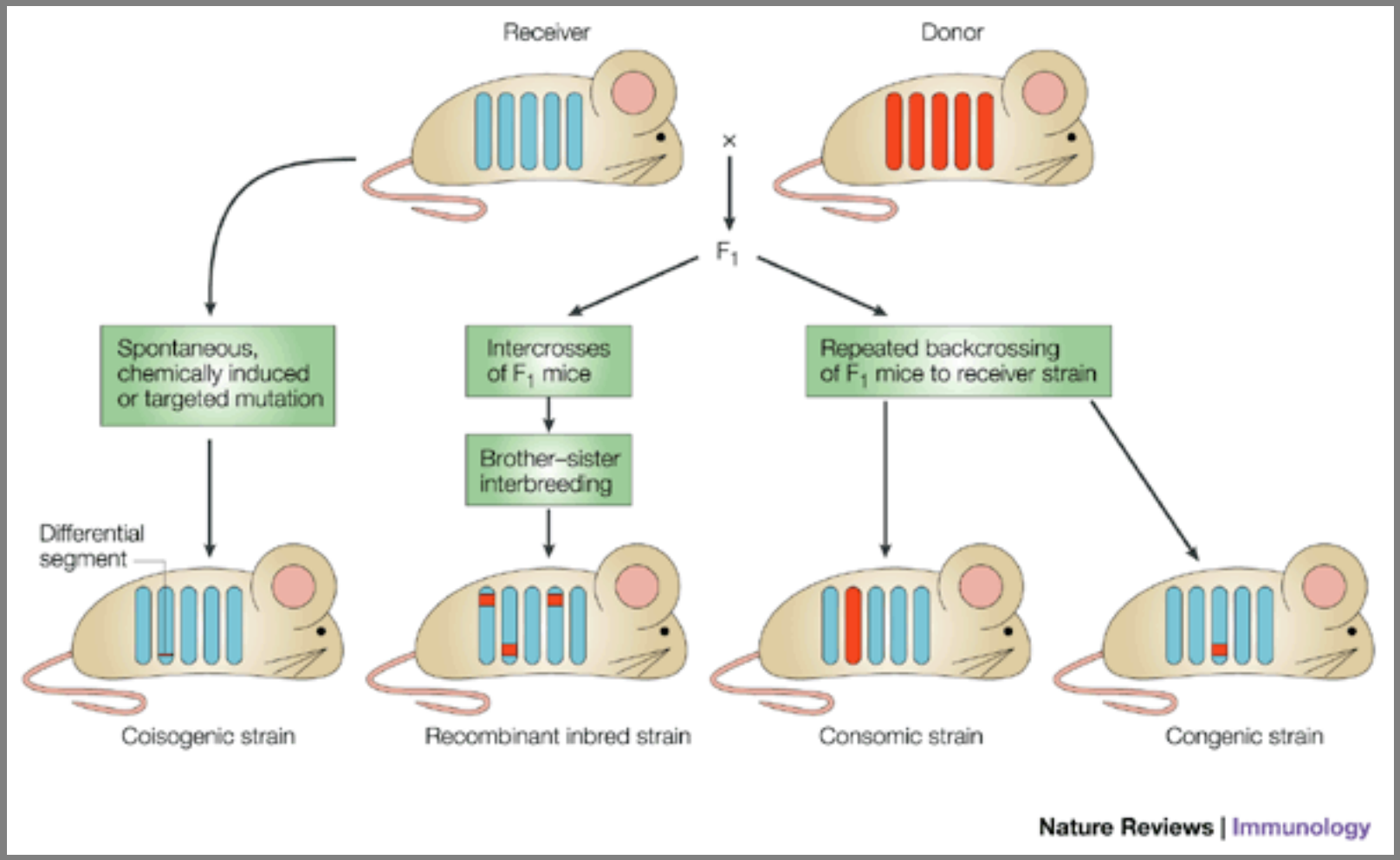
SNP ID (dbSNP Build 128)	Map Position (NCBI Build 37)	rs orient	Gene : dbSNP Function Class	Assays (ss)	Variation Type	C57BL/6J	129S1/SvImJ	Allele Summary (all strains)
rs3157349 MPD | dbSNP | MGI SNP Detail	Chr6:18122723	f	Cftr : Intron	2	SNP	A	C	A/C
rs3161305 MPD | dbSNP | MGI SNP Detail	Chr6:18122761	f	Cftr : Intron	2	SNP	T	A	A/T
rs3157350 MPD | dbSNP | MGI SNP Detail	Chr6:18122824	f	Cftr : Intron	2	SNP	A	C	A/C

Done

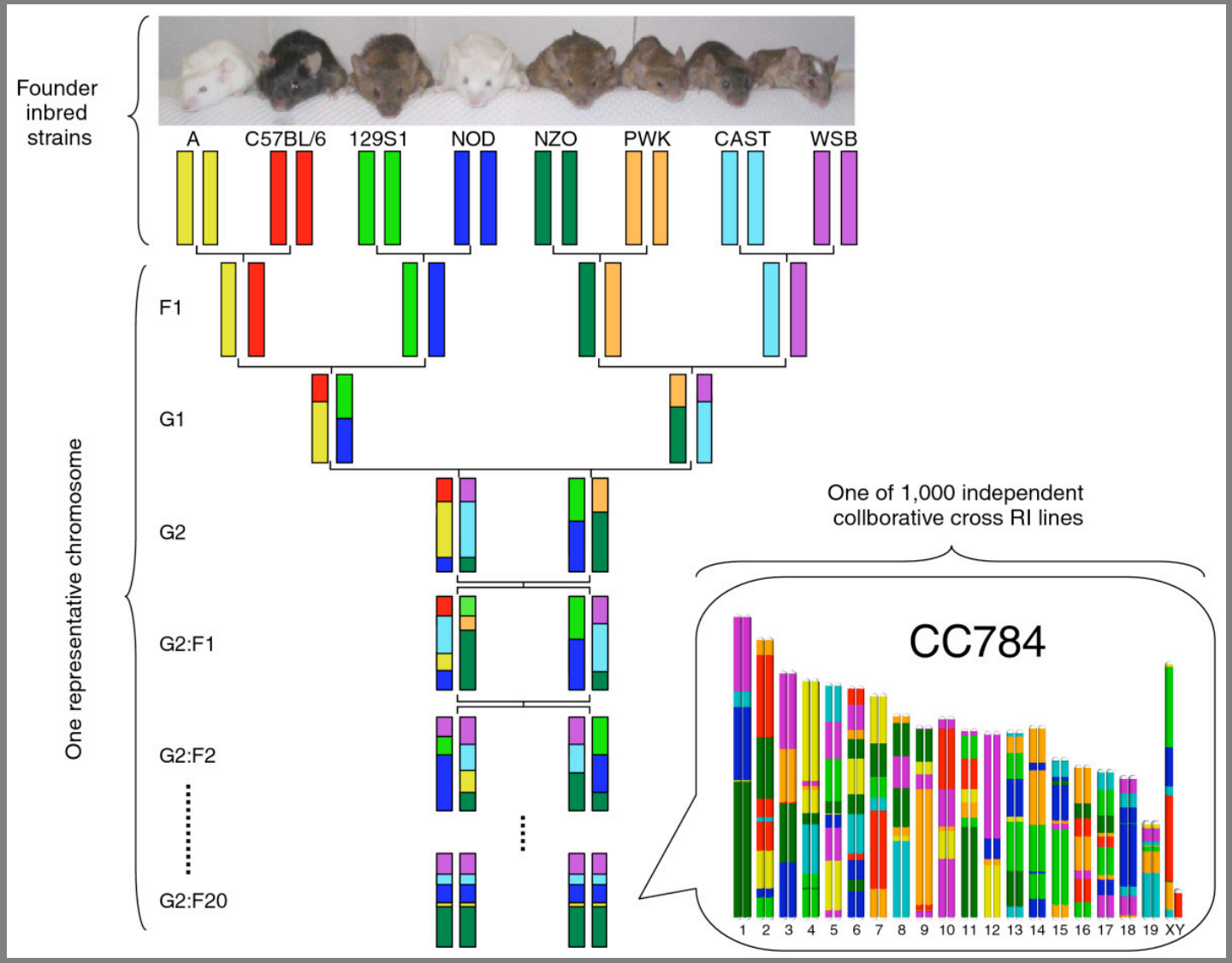
Standard Crosses

- Incross: mating between individuals of an inbred strain. Used for inbred strain maintenance.
- Outcross: mating between 2 unrelated strains. To generate F1s.
- Backcross: mating between a heterozygous F1 and one of the parent strains. Used in linkage analysis.
- Intercross: mating between two identically heterozygous individuals. Used in linkage analysis.

Designer Crosses



Collaborative Cross



http://compgen.unc.edu/wp/?page_id=99

Reference Material

- ***Mouse Genetics, Concepts and Applications* (1995) Silver, L.M. Oxford University Press, New York, NY**
- ***Genetic Variants and Strains of the Laboratory Mouse*, 3rd Edition (1996) Edited by M. F. Lyon, S. Rastan and S.D.M. Brown. Oxford University Press,New York, NY**
- **Online Books:**

  http://www.informatics.jax.org/resources.shtml#res_books
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  http://www.informatics.jax.org/resources.shtml